LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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April 25, 2005

OVERNIGHT COURIER 4/25/05

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act, and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Diphenoxylate Hydrochloride and Atropine Sulfate Tablets USP 5 mg / 0.05 mg, is suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Diphenoxylate Hydrochloride and Atropine Sulfate Tablets USP 5 mg / 0.05 mg is suitable for submission as an ANDA. The listed reference-drug product (RLD), upon which this petition is based, is Lomotil® (diphenoxylate hydrochloride and atropine sulfate) Tablets 2.5 mg / 0.025 mg by G.D. Searle (as listed in the electronic Orange Book).

B. Statement of Grounds

The Federal Food, Drug and Cosmetic Act provides for the submission of an Abbreviated New Drug Application for a drug product that differs in dosage strength from that of the listed drug provided the FDA has approved a petition that proposed filing such an application.

The RLD, Lomotil® Tablets by G.D. Searle is a tablet product containing 2.5 mg of diphenoxylate hydrochloride and 0.025 mg atropine sulfate. See listing from the electronic version of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (accessed April 25, 2005). (Attachment 1) The proposed drug product also represents a tablet dosage form, but containing 5 mg of diphenoxylate hydrochloride and 0.05 mg of atropine sulfate (twice the amount contained in the RLD). The petition is thus seeking a change in strength (from 2.5 mg / 0.025 mg per tablet to 5 mg / 0.05 mg per tablet) from that of the RLD. Please note that the proposed change in strength represents a dosage strength that, while twice the strength of the RLD, is the initial and usual recommended dosage strength in the RLD's approved labeling.

The acceptability of the proposed 5 mg / 0.05 mg strength is clearly contemplated in the approved labeling of the 2.5 mg / 0.25 mg RLD drug. The current dosing instructions in the approved labeling of the Lomotil® RLD labeling are as follows:

> *Adults:* The recommended initial dosage is two Lomotil tablets four times daily or 10 ml (two regular teaspoonfuls) of Lomotil liquid four times daily (20 mg per day). Most patients will require this dosage until initial control has been achieved, after which the dosage may be reduced to meet individual requirements. Control may often be maintained with as little as 5 mg (two tablets or 10 ml of liquid) daily.

The pediatric dosing recommendations for the RLD are as follows:

> Dosage schedule for children: The recommended initial total daily dosage of Lomotil liquid for children is 0.3 to 0.4 mg/kg, administered in four divided doses.
>
> The recommended dosage for children 13-16 years: 2 tablets or two 5 ml liquid measures three times daily.

The labeling of the approved RLD thus clearly contemplates a tablet of the strength proposed by this petition.

A double-strength tablet would permit administration of the initial and usual approved dose in a single-dosage unit and will likely improve convenience for the patient. Because the proposed product will be scored, the physician will retain the same flexibility in dosing as available with two single tablets of the RLD.

There are no proposed changes in labeling with the exception of the obvious changes in strength sought in this petition. The uses, indications, warnings and directions for use will remain the same as that of the RLD with the obvious exception as would be required by the change in the strength proposed in the petition. Draft labeling for the proposed product is included in Attachment 2. The RLD's approved labeling is provided in Attachment 3.

Therefore, the petitioner's request for the Commissioner to find that a change in strength from 2.5 mg / 0.025 mg of diphenoxylate hydrochloride and atropine sulfate per tablet to 5 mg / 0.05 mg diphenoxylate hydrochloride and atropine sulfate per tablet should raise no questions of safety or effectiveness, and the Agency should approve the petition.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis, if requested by the Agency.

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Robert W. Pollock
Vice President

RWP/pk

Attachments:
1. Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book) accessed 4/25/05
2. Draft Insert Labeling Proposed for Diphenoxylate hydrochloride and Atropine Sulfate Tablets USP, 5 mg / 0.05 mg
3. Labeling for the RLD, Lomotil® Tablets

cc: Emily Thakur (OGD)

A43P5115

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 1

Search results from the "OB_Rx" table for query on "012462."

Active Ingredient:	ATROPINE SULFATE; DIPHENOXYLATE HYDROCHLORIDE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	LOMOTIL
Applicant:	GD SEARLE LLC
Strength:	0.025MG;2.5MG
Application Number:	012462
Product Number:	001
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AA**
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through March, 2005

Patent and Generic Drug Product Data Last Updated: April 25, 2005

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

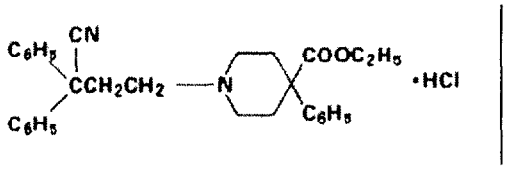
ATTACHMENT 2

Diphenoxylate hydrochloride and atropine sulfate tablets
Diphenoxylate hydrochloride and atropine sulfate liquid

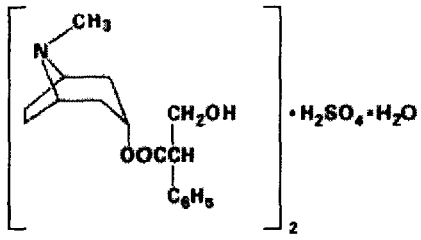
DESCRIPTION

Each diphenoxylate hydrochloride and atropine sulfate tablet and each 5 mLof diphenoxylate hydrochloride and atropine sulfate liquid for oral use contains:
diphenoxylate hydrochloride . . . . . .5.0 mg
atropine sulfate . . . . . 0.05 mg

Diphenoxylate hydrochloride, an antidiarrheal, is ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotate monohydrochloride and has the following structural formula:



Atropine sulfate, an anticholinergic, is endo-(±)-[a]-(hydroxymethyl) benzeneacetic acid 8-methyl-8-azabicyclo[3.2.1] oct-3-yl ester sulfate (2:1) (salt) monohydrate and has the following structural formula:



A subtherapeutic amount of atropine sulfate is present to discourage deliberate overdosage. Inactive ingredients of diphenoxylate hydrochloride and atropine sulfate tablets include (TBD).

CLINICAL PHARMACOLOGY

Diphenoxylate is rapidly and extensively metabolized in man by ester hydrolysis to diphenoxylic acid (difenoxine), which is biologically active and the major metabolite in the blood. After a 5-mg oral dose of carbon-14 labeled diphenoxylate hydrochloride in ethanolic solution was given to three healthy volunteers, an average of 14% of the drug plus its metabolites was excreted in the urine and 49% in the feces over a four-day period. Urinary excretion of the unmetabolized drug constituted less than 1% of the dose, and diphenoxylic acid plus its glucuronide conjugate constituted about 6% of the dose. In a 16-subject crossover bioavailability study, a linear relationship in the dose range of 2.5 to 10 mg was found between the dose of diphenoxylate hydrochloride (given as diphenoxylate hydrochloride and atropine sulfate liquid) and the peak plasma

concentration, the area under the plasma concentration-time curve, and the amount of diphenoxylic acid excreted in the urine. In the same study the bioavailability of the tablet compared with an equal dose of the liquid was approximately 90%. The average peak plasma concentration of diphenoxylic acid following ingestion of four 2.5-mg tablets was 163 ng/mL at about 2 hours, and the elimination half-life of diphenoxylic acid was approximately 12 to 14 hours. In dogs, diphenoxylate hydrochloride has a direct effect on circular smooth muscle of the bowel that conceivably results in segmentation and prolongation of gastrointestinal transit time. The clinical antidiarrheal action of diphenoxylate hydrochloride may thus be a consequence of enhanced segmentation that allows increased contact of the intraluminal contents with the intestinal mucosa.

INDICATIONS AND USAGE

Diphenoxylate hydrochloride and atropine sulfate is effective as adjunctive therapy in the management of diarrhea.

CONTRAINDICATIONS

Diphenoxylate hydrochloride and atropine sulfate is contraindicated in patients with:

1. Known hypersensitivity to diphenoxylate or atropine.
2. Obstructive jaundice.
3. Diarrhea associated with pseudomembranous enterocolitis or enterotoxin-producing bacteria.

WARNINGS

DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE IS NOT RECOMMENDED FOR CHILDREN UNDER 2 YEARS OF AGE. OVERDOSAGE MAY RESULT IN SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH (SEE *OVERDOSAGE*). THEREFORE, KEEP THIS MEDICATION OUT OF THE REACH OF CHILDREN. THE USE OF DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE SHOULD BE ACCOMPANIED BY APPROPRIATE FLUID AND ELECTROLYTE THERAPY, WHEN INDICATED. IF SEVERE DEHYDRATION OR ELECTROLYTE IMBALANCE IS PRESENT, DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE SHOULD BE WITHHELD UNTIL APPROPRIATE CORRECTIVE THERAPY HAS BEEN INITIATED. DRUGINDUCED INHIBITION OF PERISTALSIS MAY RESULT IN FLUID RETENTION IN THE INTESTINE, WHICH MAY FURTHER AGGRAVATE DEHYDRATION AND ELECTROLYTE IMBALANCE. DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE SHOULD BE USED WITH SPECIAL CAUTION IN YOUNG CHILDREN BECAUSE THIS AGE GROUP MAY BE PREDISPOSED TO DELAYED DIPHENOXYLATE TOXICITY AND

BECAUSE OF THE GREATER VARIABILITY OF RESPONSE IN THIS AGE GROUP.

Antiperistaltic agents may prolong and/or worsen diarrhea associated with organisms that penetrate the intestinal mucosa (toxigenic *E. coli, Salmonella, Shigella*), and pseudomembranous enterocolitis associated with broad-spectrum antibiotics. Antiperistaltic agents should not be used in these conditions. In some patients with acute ulcerative colitis, agents that inhibit intestinal motility or prolong intestinal transit time have been reported to induce toxic megacolon. Consequently, patients with acute ulcerative colitis should be carefully observed and diphenoxylate hydrochloride and atropine sulfate therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop. Since the chemical structure of diphenoxylate hydrochloride is similar to that of meperidine hydrochloride, the concurrent use of diphenoxylate hydrochloride and atropine sulfate with monoamine oxidase (MAO) inhibitors may, in theory, precipitate hypertensive crisis. Diphenoxylate hydrochloride and atropine sulfate should be used with extreme caution in patients with advanced hepatorenal disease and in all patients with abnormal liver function since hepatic coma may be precipitated. Diphenoxylate hydrochloride may potentiate the action of barbiturates, tranquilizers, and alcohol. Therefore, the patient should be closely observed when any of these are used concomitantly.

PRECAUTIONS

General: Since a subtherapeutic dose of atropine has been added to the diphenoxylate hydrochloride, consideration should be given to the precautions relating to the use of atropine. In children, diphenoxylate hydrochloride and atropine sulfate should be used with caution since signs of atropinism may occur even with recommended doses, particularly in patients with Down's syndrome.

Information for patients: INFORM THE PATIENT (PARENT OR GUARDIAN) NOT TO EXCEED THE RECOMMENDED DOSAGE AND TO KEEP DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE OUT OF THE REACH OF CHILDREN AND IN A CHILD-RESISTANT CONTAINER. INFORM THE PATIENT OF THE CONSEQUENCES OF OVERDOSAGE, INCLUDING SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH. Diphenoxylate hydrochloride and atropine sulfate may produce drowsiness or dizziness. The patient should be cautioned regarding activities requiring mental alertness, such as driving or operating dangerous machinery. Potentiation of the action of alcohol, barbiturates, and tranquilizers with concomitant use of diphenoxylate hydrochloride and atropine sulfate should be explained to the patient. The physician should also provide the patient with other information in this labeling, as appropriate.

Drug interactions: Known drug interactions include barbiturates, tranquilizers, and alcohol. Diphenoxylate hydrochloride and atropine sulfate may interact with MAO inhibitors (see *Warnings*). In studies with male rats, diphenoxylate hydrochloride was found to inhibit the hepatic microsomal enzyme system at a

dose of 2 mg/kg/day. Therefore, diphenoxylate has the potential to prolong the biological half-lives of drugs for which the rate of elimination is dependent on the microsomal drug metabolizing enzyme system.

Carcinogenesis, mutagenesis, impairment of fertility: No long-term study in animals has been performed to evaluate carcinogenic potential. Diphenoxylate hydrochloride was administered to male and female rats in their diets to provide dose levels of 4 and 20 mg/kg/day throughout a three-litter reproduction study. At 50 times the human dose (20 mg/kg/day), female weight gain was reduced and there was a marked effect on fertility as only 4 of 27 females became pregnant in three test breedings. The relevance of this finding to usage of diphenoxylate hydrochloride and atropine sulfate in humans is unknown.

Pregnancy: Pregnancy Category C. Diphenoxylate hydrochloride has been shown to have an effect on fertility in rats when given in doses 50 times the human dose (see above discussion). Other findings in this study include a decrease in maternal weight gain of 30% at 20 mg/kg/day and of 10% at 4 mg/kg/day. At 10 times the human dose (4 mg/kg/day), average litter size was slightly reduced. Teratology studies were conducted in rats, rabbits, and mice with diphenoxylate hydrochloride at oral doses of 0.4 to 20 mg/kg/day. Due to experimental design and small numbers of litters, embryotoxic, fetotoxic, or teratogenic effects cannot be adequately assessed. However, examination of the available fetuses did not reveal any indication of teratogenicity. There are no adequate and well-controlled studies in pregnant women. Diphenoxylate hydrochloride and atropine sulfate should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing mothers: Caution should be exercised when diphenoxylate hydrochloride and atropine sulfate is administered to a nursing woman, since the physicochemical characteristics of the major metabolite, diphenoxylic acid, are such that it may be excreted in breast milk and since it is known that atropine is excreted in breast milk.

Pediatric use: Diphenoxylate hydrochloride and atropine sulfate may be used as an adjunct to the treatment of diarrhea but should be accompanied by appropriate fluid and electrolyte therapy, if needed. DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE IS NOT RECOMMENDED FOR CHILDREN UNDER 2 YEARS OF AGE. Diphenoxylate hydrochloride and atropine sulfate should be used with special caution in young children because of the greater variability of response in this age group. See *Warnings* and *Dosage and Administration.* In case of accidental ingestion by children, see *Overdosage* for recommended treatment.

ADVERSE REACTIONS

At *therapeutic* doses, the following have been reported; they are listed in decreasing order of severity, but not of frequency:

Nervous system: numbness of extremities, euphoria, depression, malaise/lethargy, confusion, sedation/drowsiness, dizziness, restlessness, headache.

Allergic: anaphylaxis, angioneurotic edema, urticaria, swelling of the gums, pruritus.
Gastrointestinal system: toxic megacolon, paralytic ileus, pancreatitis, vomiting, nausea, anorexia, abdominal discomfort.
The following atropine sulfate effects are listed in decreasing order of severity, but not of frequency: hyperthermia, tachycardia, urinary retention, flushing, dryness of the skin and mucous membranes. These effects may occur, especially in children.
THIS MEDICATION SHOULD BE KEPT IN A CHILD-RESISTANT CONTAINER AND OUT OF THE REACH OF CHILDREN SINCE AN OVERDOSAGE MAY RESULT IN SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH.

DRUG ABUSE AND DEPENDENCE

Controlled substance: Diphenoxylate hydrochloride and atropine sulfate is classified as a Schedule V controlled substance by federal regulation. Diphenoxylate hydrochloride is chemically related to the narcotic analgesic meperidine.
Drug abuse and dependence: In doses used for the treatment of diarrhea, whether acute or chronic, diphenoxylate has not produced addiction. Diphenoxylate hydrochloride is devoid of morphine-like subjective effects at therapeutic doses. At high doses it exhibits codeine-like subjective effects. The dose which produces antidiarrheal action is widely separated from the dose which causes central nervous system effects. The insolubility of diphenoxylate hydrochloride in commonly available aqueous media precludes intravenous self-administration. A dose of 100 to 300 mg/day, which is equivalent to 20 to 60 tablets, administered to humans for 40 to 70 days, produced opiate withdrawal symptoms. Since addiction to diphenoxylate hydrochloride is possible at high doses, the recommended dosage should not be exceeded.

OVERDOSAGE

RECOMMENDED DOSAGE SCHEDULES SHOULD BE STRICTLY FOLLOWED. THIS MEDICATION SHOULD BE KEPT IN A CHILD-RESISTANT CONTAINER AND OUT OF THE REACH OF CHILDREN, SINCE AN OVERDOSAGE MAY RESULT IN SEVERE, EVEN FATAL, RESPIRATORY DEPRESSION.

Diagnosis: Initial signs of overdosage may include dryness of the skin and mucous membranes, mydriasis, restlessness, flushing, hyperthermia, and tachycardia followed by lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, and respiratory depression. Respiratory depression may be evidenced as late as 30 hours after ingestion and may recur despite an initial response to narcotic antagonists. TREAT ALL POSSIBLE DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE OVERDOSAGES AS SERIOUS AND MAINTAIN MEDICAL OBSERVATION FOR AT LEAST 48 HOURS, PREFERABLY UNDER CONTINUOUS HOSPITAL CARE.

Treatment: In the event of overdose, induction of vomiting, gastric lavage, establishment of a patent airway, and possibly mechanically assisted respiration are advised. *In vitro* and animal studies indicate that activated charcoal may significantly decrease the bioavailability of diphenoxylate. In noncomatose patients, a slurry of 100 g of activated charcoal can be administered immediately after the induction of vomiting or gastric lavage. A pure narcotic antagonist (eg, naloxone) should be used in the treatment of respiratory depression caused by diphenoxylate hydrochloride and atropine sulfate. When a narcotic antagonist is administered intravenously, the onset of action is generally apparent within two minutes. It may also be administered subcutaneously or intramuscularly, providing a slightly less rapid onset of action but a more prolonged effect. To counteract respiratory depression caused by diphenoxylate hydrochloride and atropine sulfate overdosage, the following dosage schedule for the narcotic antagonist naloxone hydrochloride should be followed:

Adult dosage: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2- to 3-minute intervals. If no response is observed after 10 mg of naloxone hydrochloride has been administered, the diagnosis of narcotic-induced or partial narcotic-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Children: The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, naloxone hydrochloride may be administered I.M. or S.C. in divided doses. If necessary, naloxone hydrochloride can be diluted with sterile water for injection. Following initial improvement of respiratory function, repeated doses of naloxone hydrochloride may be required to counteract recurrent respiratory depression. Supplemental intramuscular doses of naloxone hydrochloride may be utilized to produce a longer-lasting effect. Since the duration of action of diphenoxylate hydrochloride is longer than that of naloxone hydrochloride, improvement of respiration following administration may be followed by recurrent respiratory depression. Consequently, continuous observation is necessary until the effect of diphenoxylate hydrochloride on respiration has passed. This effect may persist for many hours. The period of observation should extend over at least 48 hours, preferably under continuous hospital care. Although signs of overdosage and respiratory depression may not be evident soon after ingestion of diphenoxylate hydrochloride, respiratory depression may occur from 12 to 30 hours later.

DOSAGE AND ADMINISTRATION

DO NOT EXCEED RECOMMENDED DOSAGE.

Adults: The recommended initial dosage is one diphenoxylate hydrochloride and atropine sulfate tablet four times daily or 5 mL (one regular teaspoonful) of diphenoxylate hydrochloride and atropine sulfate liquid four times daily (20 mg per day). Most patients will require this dosage until initial control has been achieved, after which the dosage may be reduced to meet individual requirements. Control may often be maintained with as little as 5 mg (one tablet or 5 mL of liquid) daily. Clinical improvement of acute diarrhea is usually observed within 48 hours. If clinical improvement of chronic diarrhea after treatment with a maximum daily dose of 20 mg of diphenoxylate hydrochloride is not observed within 10 days, symptoms are unlikely to be controlled by further administration.

Children: Diphenoxylate hydrochloride and atropine sulfate is not recommended in children under 2 years of age and should be used with special caution in young children (see *Warnings* and *Precautions*). *The nutritional status and degree of dehydration must be considered. In children under 13 years of age, use diphenoxylate hydrochloride and atropine sulfate liquid. Do not use diphenoxylate hydrochloride and atropine sulfate tablets for this age group.*

Only the plastic dropper should be used when measuring Diphenoxylate hydrochloride and atropine sulfate liquid for administration to children.

Dosage schedule for children: The recommended initial total daily dosage of diphenoxylate hydrochloride and atropine sulfate liquid for children is 0.3 to 0.4 mg/kg, administered in four divided doses. The following table provides an *approximate* initial daily dosage recommendation for children.

Age (years)	**Approximate weight (kg)**	**(lb)**	**Dosage in mL (Four times daily)**
2	**11-14**	**24-31**	**.75 - 1.5**
3	**12-16**	**26-35**	**1.0 - 1.5**
4	**14-20**	**31-44**	**1.0 – 2.0**
5	**16-23**	**35-51**	**1.25 –2.25**
6-8	**17-32**	**38-71**	**1.25 – 2.5**
9-12	**29-55**	**51-121**	**1.75 – 2.5**

The recommended dosage for children 13–16 years: 1 tablet or one 5 mL liquid measure three times daily. These pediatric schedules are the best approximation of an average dose recommendation which may be adjusted downward according to the overall nutritional status and degree of dehydration encountered in the sick child. Reduction of dosage may be made as soon as initial control of symptoms has been achieved. Maintenance dosage may be as low as one-fourth of the initial daily dosage. If no response occurs within 48 hours, diphenoxylate hydrochloride and atropine sulfate is unlikely to be effective. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

HOW SUPPLIED

Tablets — round, white, with [TBD] debossed on one side and [TBD] on the other side and containing 5.0 mg of diphenoxylate hydrochloride and 0.05 mg of atropine sulfate, supplied as:

NDC Number	Size
[TBD]	bottle of XXX
[TBD]	bottle of XXX
[TBD]	bottle of XXX

Liquid—containing 5.0 mg of diphenoxylate hydrochloride and 0.05 mg of atropine sulfate per 5 mL; bottles of [TBD] fl oz (NDC Number [TBD]). Dispense only in original container. A plastic dropper calibrated in increments of 1/4 mL (1/4 mg) with a capacity of 1 mL (1 mg) accompanies each [TBD]-oz bottle of diphenoxylate hydrochloride and atropine sulfate liquid. Only this plastic dropper should be used when measuring diphenoxylate hydrochloride and atropine sulfate liquid for administration to children.

Rx only Revised: [TBD]

[Manufacturer Name & Address]

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 3

Lomotil® ℞

diphenoxylate hydrochloride and atropine sulfate tablets

diphenoxylate hydrochloride and atropine sulfate liquid

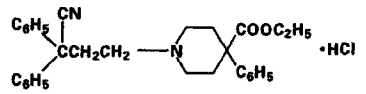
DESCRIPTION

Each Lomotil tablet and each 5 ml of Lomotil liquid for oral use contains:

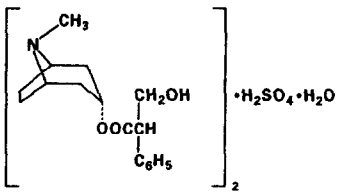
diphenoxylate hydrochloride . . . . . .2.5 mg

atropine sulfate . . . . . .0.025 mg

Diphenoxylate hydrochloride, an antidiarrheal, is ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotate monohydrochloride and has the following structural formula:



Atropine sulfate, an anticholinergic, is endo-(±)-α-(hydroxymethyl) benzeneacetic acid 8-methyl-8-azabicyclo[3.2.1] oct-3-yl ester sulfate (2:1) (salt) monohydrate and has the following structural formula:



A subtherapeutic amount of atropine sulfate is present to discourage deliberate overdosage.

Inactive ingredients of Lomotil tablets include acacia, corn starch, magnesium stearate, sorbitol, sucrose, and talc. Inactive ingredients of Lomotil liquid include cherry flavor, citric acid, ethyl alcohol 15%, FD&C Yellow No. 6, glycerin, sodium phosphate, sorbitol, and water.

CLINICAL PHARMACOLOGY

Diphenoxylate is rapidly and extensively metabolized in man by ester hydrolysis to diphenoxylic acid (difenoxine), which is biologically active and the major metabolite in the blood. After a 5-mg oral dose of carbon-14 labeled diphenoxylate hydrochloride in ethanolic solution was given to three healthy volunteers, an average of 14% of the drug plus its metabolites was excreted in the urine and 49% in the feces over a four-day period. Urinary excretion of the unmetabolized drug constituted less than 1% of the dose, and diphenoxylic acid plus its glucuronide conjugate constituted about 6% of the dose. In a 16-subject crossover bioavailability study, a linear relationship in the dose range of 2.5 to 10 mg was found between the dose of diphenoxylate hydrochloride (given as Lomotil liquid) and the peak plasma concentration, the area under the plasma concentration-time curve, and the amount of diphenoxylic acid excreted in the urine. In the same study the bioavailability of the tablet compared with an equal dose of the liquid was approximately 90%. The average peak plasma concentration of diphenoxylic acid following ingestion of four 2.5-mg tablets was 163 ng/ml at about 2 hours, and the elimination half-life of diphenoxylic acid was approximately 12 to 14 hours.

In dogs, diphenoxylate hydrochloride has a direct effect on circular smooth muscle of the

diphenoxylate hydrochloride and atropine sulfate tablets
diphenoxylate hydrochloride and atropine sulfate liquid
Lomotil® ℞
P04009 818 929 000

Lomotil

diphenoxylate hydrochloride and atropine sulfate tablets

diphenoxylate hydrochloride and atropine sulfate liquid

bowel that conceivably results in segmentation and prolongation of gastrointestinal transit time. The clinical antidiarrheal action of diphenoxylate hydrochloride may thus be a consequence of enhanced segmentation that allows increased contact of the intraluminal contents with the intestinal mucosa.

INDICATIONS AND USAGE

Lomotil is effective as adjunctive therapy in the management of diarrhea.

CONTRAINDICATIONS

Lomotil is contraindicated in patients with

1. Known hypersensitivity to diphenoxylate or atropine.
2. Obstructive jaundice.
3. Diarrhea associated with pseudomembranous enterocolitis or enterotoxin-producing bacteria.

WARNINGS

LOMOTIL IS *NOT* AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. LOMOTIL IS NOT RECOMMENDED FOR CHILDREN UNDER 2 YEARS OF AGE. OVERDOSAGE MAY RESULT IN SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH (SEE *OVERDOSAGE*). THEREFORE, KEEP THIS MEDICATION OUT OF THE REACH OF CHILDREN.

THE USE OF LOMOTIL SHOULD BE ACCOMPANIED BY APPROPRIATE FLUID AND ELECTROLYTE THERAPY, WHEN INDICATED. IF SEVERE DEHYDRATION OR ELECTROLYTE IMBALANCE IS PRESENT, LOMOTIL SHOULD BE WITHHELD UNTIL APPROPRIATE CORRECTIVE THERAPY HAS BEEN INITIATED. DRUG-INDUCED INHIBITION OF PERISTALSIS MAY RESULT IN FLUID RETENTION IN THE INTESTINE, WHICH MAY FURTHER AGGRAVATE DEHYDRATION AND ELECTROLYTE IMBALANCE.

LOMOTIL SHOULD BE USED WITH SPECIAL CAUTION IN YOUNG CHILDREN BECAUSE THIS AGE GROUP MAY BE PREDISPOSED TO DELAYED DIPHENOXYLATE TOXICITY AND BECAUSE OF THE GREATER VARIABILITY OF RESPONSE IN THIS AGE GROUP.

Antiperistaltic agents may prolong and/or worsen diarrhea associated with organisms that penetrate the intestinal mucosa (toxigenic *E. coli, Salmonella, Shigella*), and pseudomembranous enterocolitis associated with broad-spectrum antibiotics. Antiperistaltic agents should not be used in these conditions.

In some patients with acute ulcerative colitis, agents that inhibit intestinal motility or prolong intestinal transit time have been reported to induce toxic megacolon. Consequently, patients with acute ulcerative colitis should be carefully observed and Lomotil therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop.

Since the chemical structure of diphenoxylate hydrochloride is similar to that of meperidine hydrochloride, the concurrent use of Lomotil with monoamine oxidase (MAO) inhibitors may, in theory, precipitate hypertensive crisis.

Lomotil should be used with extreme caution in patients with advanced hepatorenal disease and in all patients with abnormal liver function since hepatic coma may be precipitated.

Diphenoxylate hydrochloride may potentiate the action of barbiturates, tranquilizers, and alcohol. Therefore, the patient should be closely observed when any of these are used concomitantly.

Lomotil

diphenoxylate hydrochloride and atropine sulfate tablets

diphenoxylate hydrochloride and atropine sulfate liquid

PRECAUTIONS

General: Since a subtherapeutic dose of atropine has been added to the diphenoxylate hydrochloride, consideration should be given to the precautions relating to the use of atropine. In children, Lomotil should be used with caution since signs of atropinism may occur even with recommended doses, particularly in patients with Down's syndrome.

Information for patients: INFORM THE PATIENT (PARENT OR GUARDIAN) NOT TO EXCEED THE RECOMMENDED DOSAGE AND TO KEEP LOMOTIL OUT OF THE REACH OF CHILDREN AND IN A CHILD-RESISTANT CONTAINER. INFORM THE PATIENT OF THE CONSEQUENCES OF OVERDOSAGE, INCLUDING SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH. Lomotil may produce drowsiness or dizziness. The patient should be cautioned regarding activities requiring mental alertness, such as driving or operating dangerous machinery. Potentiation of the action of alcohol, barbiturates, and tranquilizers with concomitant use of Lomotil should be explained to the patient. The physician should also provide the patient with other information in this labeling, as appropriate.

Drug interactions: Known drug interactions include barbiturates, tranquilizers, and alcohol. Lomotil may interact with MAO inhibitors (see *Warnings*).

In studies with male rats, diphenoxylate hydrochloride was found to inhibit the hepatic microsomal enzyme system at a dose of 2 mg/kg/day. Therefore, diphenoxylate has the potential to prolong the biological half-lives of drugs for which the rate of elimination is dependent on the microsomal drug metabolizing enzyme system.

Carcinogenesis, mutagenesis, impairment of fertility: No long-term study in animals has been performed to evaluate carcinogenic potential. Diphenoxylate hydrochloride was administered to male and female rats in their diets to provide dose levels of 4 and 20 mg/kg/day throughout a three-litter reproduction study. At 50 times the human dose (20 mg/kg/day), female weight gain was reduced and there was a marked effect on fertility as only 4 of 27 females became pregnant in three test breedings. The relevance of this finding to usage of Lomotil in humans is unknown.

Pregnancy: Pregnancy Category C. Diphenoxylate hydrochloride has been shown to have an effect on fertility in rats when given in doses 50 times the human dose (see above discussion). Other findings in this study include a decrease in maternal weight gain of 30% at 20 mg/kg/day and of 10% at 4 mg/kg/day. At 10 times the human dose (4 mg/kg/day), average litter size was slightly reduced.

Teratology studies were conducted in rats, rabbits, and mice with diphenoxylate hydrochloride at oral doses of 0.4 to 20 mg/kg/day. Due to experimental design and small numbers of litters, embryotoxic, fetotoxic, or teratogenic effects cannot be adequately assessed. However, examination of the available fetuses did not reveal any indication of teratogenicity.

There are no adequate and well-controlled studies in pregnant women. Lomotil should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing mothers: Caution should be exercised when Lomotil is administered to a nursing woman, since the physicochemical characteristics of the major metabolite, diphenoxylic acid,

or coma, hypotonic reflexes, nystagmus, pinpoint pupils, and respiratory depression. Respiratory depression may be evidenced as late as 30 hours after ingestion and may recur despite an initial response to narcotic antagonists. TREAT ALL POSSIBLE LOMOTIL OVERDOSAGES AS SERIOUS AND MAINTAIN MEDICAL OBSERVATION FOR AT LEAST 48 HOURS, PREFERABLY UNDER CONTINUOUS HOSPITAL CARE.

Treatment: In the event of overdose, induction of vomiting, gastric lavage, establishment of a patent airway, and possibly mechanically assisted respiration are advised. *In vitro* and animal studies indicate that activated charcoal may significantly decrease the bioavailability of diphenoxylate. In noncomatose patients, a slurry of 100 g of activated charcoal can be administered immediately after the induction of vomiting or gastric lavage.

A pure narcotic antagonist (eg, naloxone) should be used in the treatment of respiratory depression caused by Lomotil. When a narcotic antagonist is administered intravenously, the onset of action is generally apparent within two minutes. It may also be administered subcutaneously or intramuscularly, providing a slightly less rapid onset of action but a more prolonged effect.

To counteract respiratory depression caused by Lomotil overdosage, the following dosage schedule for the narcotic antagonist naloxone hydrochloride should be followed:

Adult dosage: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2- to 3-minute intervals. If no response is observed after 10 mg of naloxone hydrochloride has been administered, the diagnosis of narcotic-induced or partial narcotic-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Children: The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, naloxone hydrochloride may be administered I.M. or S.C. in divided doses. If necessary, naloxone hydrochloride can be diluted with sterile water for injection.

Following initial improvement of respiratory function, repeated doses of naloxone hydrochloride may be required to counteract recurrent respiratory depression. Supplemental intramuscular doses of naloxone hydrochloride may be utilized to produce a longer-lasting effect.

Since the duration of action of diphenoxylate hydrochloride is longer than that of naloxone hydrochloride, improvement of respiration following administration may be followed by recurrent respiratory depression. Consequently, continuous observation is necessary until the effect of diphenoxylate hydrochloride on respiration has passed. This effect may persist for many hours. The period of observation should extend over at least 48 hours, preferably under continuous hospital care. Although signs of overdosage and respiratory depression may not be evident soon after ingestion of diphenoxylate hydrochloride, respiratory depression may occur from 12 to 30 hours later.

DOSAGE AND ADMINISTRATION

DO NOT EXCEED RECOMMENDED DOSAGE.

Lomotil

diphenoxylate hydrochloride and atropine sulfate tablets

diphenoxylate hydrochloride and atropine sulfate liquid

Adults: The recommended initial dosage is two Lomotil tablets four times daily or 10 ml (two regular teaspoonfuls) of Lomotil liquid four times daily (20 mg per day). Most patients will require this dosage until initial control has been achieved, after which the dosage may be reduced to meet individual requirements. Control may often be maintained with as little as 5 mg (two tablets or 10 ml of liquid) daily.

Clinical improvement of acute diarrhea is usually observed within 48 hours. If clinical improvement of chronic diarrhea after treatment with a maximum daily dose of 20 mg of diphenoxylate hydrochloride is not observed within 10 days, symptoms are unlikely to be controlled by further administration.

Children: Lomotil is not recommended in children under 2 years of age and should be used with special caution in young children (see Warnings and Precautions). The nutritional status and degree of dehydration must be considered. In children under 13 years of age, use Lomotil liquid. Do not use Lomotil tablets for this age group.

Only the plastic dropper should be used when measuring Lomotil liquid for administration to children.

Dosage schedule for children: The recommended initial total daily dosage of Lomotil liquid for children is 0.3 to 0.4 mg/kg, administered in four divided doses. The following table provides an *approximate* initial daily dosage recommendation for children.

Age (years)	Approximate weight (kg)	(lb)	Dosage in ml (four times daily)
2	11–14	24–31	1.5–3.0
3	12–16	26–35	2.0–3.0
4	14–20	31–44	2.0–4.0
5	16–23	35–51	2.5–4.5
6–8	17–32	38–71	2.5–5.0
9–12	23–55	51–121	3.5–5.0

The recommended dosage for children 13–16 years: 2 tablets or two 5 ml liquid measures three times daily.

These pediatric schedules are the best approximation of an average dose recommendation which may be adjusted downward according to the overall nutritional status and degree of dehydration encountered in the sick child. Reduction of dosage may be made as soon as initial control of symptoms has been achieved. Maintenance dosage may be as low as one-fourth of the initial daily dosage. If no response occurs within 48 hours, Lomotil is unlikely to be effective.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

HOW SUPPLIED

Tablets — round, white, with SEARLE debossed on one side and 61 on the other side and containing 2.5 mg of diphenoxylate hydrochloride and 0.025 mg of atropine sulfate, supplied as:

NDC Number	Size
0025-0061-31	bottle of 100
0025-0061-51	bottle of 500
0025-0061-52	bottle of 1,000
0025-0061-55	bottle of 2,500
0025-0061-34	carton of 100 unit dose

Liquid—containing 2.5 mg of diphenoxylate hydrochloride and 0.025 mg of atropine sulfate per 5 ml; bottles of 2 fl oz (NDC Number 0025-0066-02). Dispense only in original container.

A plastic dropper calibrated in increments of

Lomotil

diphenoxylate hydrochloride and atropine sulfate tablets

diphenoxylate hydrochloride and atropine sulfate liquid

1/2 ml (1/4 mg) with a capacity of 2 ml (1 mg) accompanies each 2-oz bottle of Lomotil liquid. Only this plastic dropper should be used when measuring Lomotil liquid for administration to children.

℞ only Revised: September 2001

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PHARMACIA

Lomotil® ℂ

diphenoxylate hydrochloride and atropine sulfate tablets

diphenoxylate hydrochloride and atropine sulfate liquid

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